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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/756,070	Taylor
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 13, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above, claim(s) *43-63 and 69-71* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 6-32, 34-42, 64-68, and 72* is/are rejected.

7) ☒ Claim(s) *5 and 33* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 1
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Priority

1. This application is claiming the benefit of a prior filed nonprovisional application 09/687,834 under 35 U.S.C. 120, 121, or 365(c). The application 09/687,834 has been abandoned on October 11, 2000, whereas the filing date of the current application is January 6, 2001. Therefore, priority to the application 09/687,834 is not granted as copendency between the current application and the prior application is required.

Election/Restriction

2. Applicant's election without traverse of Group I in Paper No. 0503 is acknowledged.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 65 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 65 is dependent on non-elected and therefore non-existent claim 63. It is not clear what are the metes and bounds of claim 65. The claim is therefore vague and indefinite.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 7-13, 17-36, 38- 42, 64, 66, 67, and 68 are rejected under 35 U.S.C. 103(a) over Ohmiya et al. (Analytical Biochemistry, (1990), Vol. 189, pages 126-130) in view of Gjerde et al. (U.S. Patent 5,972,222) (October 26, 1999).

Ohmiya et al teaches the separation of various types of DNA molecules and their fragments of various sizes by (a) applying the mixture of DNA molecules to an anion-exchange solid (Abstract, Figures 1-6, and RESULTS AND DISCUSSION Section).

Ohmiya et al does not teach a chromatographic method for separating heteroduplex and homoduplex DNA molecules in a mixture.

Gjerde et al teaches a chromatographic method for separating heteroduplex and homoduplex DNA molecules in a mixture (Example 7, and Figures 14 and 15), the method comprising:

eluting the solid of ion exchange column with a mobile phase comprising an eluting salt, an organic solvent, and a buffer, wherein the eluting is carried out under conditions effective to at least partially denature the heteroduplexes and wherein the eluting results in the separation of the heteroduplexes from the homoduplexes (Column 13, line 66 to Column 14, line 15 and Example 7, and Figures 14 and 15).

Gjerde et al also suggests the step a) of the application of the mixture to an anion - exchange solid (Column 1, lines 39-49).

Ohmiya et al teaches the method, wherein the elution buffer includes contacting the solid of step (a) with a mobile phase possessing a pH in the range of 4 to 9 (pH 8.0 to be precise, page 127, Column 1, line 2), the mobile phase comprising:

an eluting salt composed of an anion selected from chloride and wherein the concentration of eluting salt is systematically increased from approximately 0.1 M to approximately 1.0 M.

Ohmiya et al does not teach a chromatographic method, wherein the eluting salt comprises a cation selected from di or trialkylammonium and a buffer acid with a pKa in the approximate range of 3.5 to 9.5, and an organic solvent.

Gjerde et al teaches a chromatographic method, wherein the eluting salt comprises a cation selected from di or trialkylammonium and a buffer acid with a pKa in the approximate range of 3.5 to 9.5, and an organic solvent.(Column 14, lines 45-67, and acetic acid buffer in Example 7, which is well known in the art to have a pKa= 4.76).

Ohmiya et al teaches the method, wherein the mobile phase includes a metal chelating agent EDTA, the cation comprises sodium and the solid is comprised of a non-porous synthetic polyolefin backbone (MATERIALS AND METHODS Section, Chromatography Subsection).

Ohmiya et al does not teach a chromatographic method, wherein the mobile phase contains an organic solvent acetonitrile, which is less than about 40% by volume of the organic solvent.

Gjerde et al teaches a chromatographic method, wherein the mobile phase contains an organic solvent acetonitrile, which is less than about 40% by volume of the organic solvent. (Column 18, lines 50-57).

Ohmiya et al teaches a chromatographic method, wherein the concentration of the eluting salt is continuously increased (Figures 1-7).

Ohmiya et al teaches a chromatographic method including analyzing the mobile phase after the elution step for the concentration of the DNA molecules by UV absorbance in the approximate wavelength range of about 250 nm to about 290 nm (Figures 1-7).

Ohmiya et al does not teach a chromatographic method, wherein the concentration of the organic solvent is systematically increased.

Gjerde et al teaches a chromatographic method, wherein the concentration of the organic solvent is systematically increased (Column 14, lines 45-67).

Ohmiya et al teaches the method, wherein the solid is contained in a column of cylindrical geometry (MATERIALS AND METHODS Section, Chromatography Subsection).

Ohmiya et al does not teach a chromatographic method, wherein the eluting is carried out at a column temperature greater than about 50 degree centigrade and in between 40 to 80 degree centigrade.

Gjerde et al teaches a chromatographic method, wherein the eluting is carried out at a column temperature greater than about 50 degree centigrade and in between 40 to 80 degree centigrade (56 degree centigrade to be precise, Column 5, lines 1-4 and Figure 14).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method in which homoduplex and heteroduplex double stranded polynucleotides are separated of Gjerde et al. in the high-resolution anion exchange chromatographic method of Ohmiya et al. since Gjerde et al states, "The methods used to capture multivalent cations and prevent their presence in the batch process described hereinabove, are essential in order to achieve high resolution separations of polynucleotides, especially double stranded DNA, and also to greatly extend the useful life of the separation media (Column 15, lines 10-15)". Further motivation is provided by Ohmiya et al as Ohmiya et al states, "In view of time efficiency, recovery, and resolution, the nonporous QA column is superior to other porous ion-exchange columns and expected to be a very useful tool in molecular biological studies (Abstract, last sentence)". An ordinary practitioner would have been motivated to combine and substitute the method in which homoduplex and heteroduplex double stranded polynucleotides are separated of Gjerde et al. in the high-resolution anion exchange chromatographic method of Ohmiya et al. in order to achieve the express advantages, as noted by

Gjerde et al., of an invention which provides a method to achieve high resolution separations of polynucleotides, especially double stranded DNA, and also to achieve the express advantages, as noted by Ohmiya et al., of the nonporous QA column which is superior to other porous ion-exchange columns and expected to be a very useful tool in molecular biological studies in view of time efficiency, recovery, and resolution.

Ohmiya et al. in view of Gjerde et al do not teach a method, wherein the total time required to complete the method is between about 2 minutes and about 30 minutes.

However, it is *prima facie* obvious that selection of the specific time to finish a polynucleotide purification procedure represents routine optimization with regard to the amount of DNA molecules present in the sample to be purified and the flow rate of the columns which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific time to finish the polynucleotide purification procedure was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

7. Claims 6, 37, and 72 are rejected under 35 U.S.C. 103(a) as being obvious over Ohmiya et al. (Analytical Biochemistry, (1990), Vol. 189, pages 126-130) in view of Gjerde et al. (U.S. Patent 5,972,222) (October 26, 1999) further in view of Bertling (U.S. Patent 6,306,592 B1) (October 23, 2001).

Ohmiya et al. in view of Gjerde et al. teach a method of claims 1-4, 7-13, 17-36, 38- 42, 64, 66, 67, and 68 as described above.

Ohmiya et al. in view of Gjerde et al do not teach a method, wherein the cation comprises guanidinium.

Bertling teaches a method, wherein the cation comprises guanidinium (Example 1, Column 6, lines 9-48).

Ohmiya et al. in view of Gjerde et al do not teach a method, wherein prior to the applying step the DNA molecules are amplified using the polymerase chain reaction and the amplified DNA molecules are denatured and renatured to form a mixture of heteroduplexe and homoduplex DNA molecules.

Bertling teaches a method, wherein prior to the applying step the DNA molecules are amplified using the polymerase chain reaction and the amplified DNA molecules are denatured and renatured to form a mixture of heteroduplex and homoduplex DNA molecules (Column 4, line 61 to Column 5, line 32 and Claim 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time

the invention was made to combine and substitute the method, wherein the cation comprises guanidinium and wherein prior to the applying step the DNA molecules are amplified using the polymerase chain reaction and the amplified DNA molecules are denatured and renatured to form a mixture of heteroduplex and homoduplex DNA molecules of Bertling in the high-resolution anion exchange chromatographic method of Ohmiya et al in view of Gjerde et al since Bertling states, "The method is especially sensitive when the purification step comprises a chromatographic purification method. The chromatographic purification method may be a column or batch method which is carried out using matrices such as silica gel or DEAE material, all of which allow a separation on the principle of ion exchange, affinity or size exclusion (Column 4, lines 4-9)". Further motivation is provided by Bertling as Bertling states, "Finally, the object according to the invention is achieved by the use of heteroduplexes for revealing and quantifying NA molecules within a population of NA molecules of identical, similar or differing sequences (Column 4, lines 18-21)". An ordinary practitioner would have been motivated to combine and substitute the method wherein the cation comprises guanidinium and wherein prior to the applying step the DNA molecules are amplified using the polymerase chain reaction and the amplified DNA molecules are denatured and renatured to form a mixture of heteroduplex and homoduplex DNA molecules of Bertling in the high-resolution anion exchange chromatographic method of Ohmiya et al in view of Gjerde et al. in order to achieve the express advantages, as noted by Bertling, of an invention which provides an especially sensitive method when the purification step comprises a chromatographic purification method and wherein the object is achieved by the use of

heteroduplexes for revealing and quantifying NA molecules within a population of NA molecules of identical, similar or differing sequences.

8. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over Ohmiya et al. (Analytical Biochemistry, (1990), Vol. 189, pages 126-130) in view of Gjerde et al. (U.S. Patent 5,972,222) (October 26, 1999) further in view of Cohen et al. (U.S. patent 5,506,103) (April 9, 1996).

Ohmiya et al. in view of Gjerde et al. teach a method of claims 1-4, 7-13, 17-36, 38- 42, 64, 66, 67, and 68 as described above.

Ohmiya et al. in view of Gjerde et al do not teach a method, wherein the solid comprises diethylaminoethyl and polyethyleneimine functional groups.

Cohen et al. teaches a method, wherein the solid comprises diethylaminoethyl and polyethyleneimine functional groups (Column 6, lines 5-6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the solid comprises diethylaminoethyl and polyethyleneimine functional groups of Cohen et al. in the high-resolution anion exchange chromatographic method of Ohmiya et al in view of Gjerde et al since Cohen et al. states, "Another useful resin is a weak anion exchange resin such as diethylaminoethyl and polyethyleneimine (Column 6, lines 5-6) ". An ordinary practitioner would have been motivated to combine and substitute the method wherein the solid comprises diethylaminoethyl and polyethyleneimine functional groups of Cohen et al. in the high-resolution anion exchange

chromatographic method of Ohmiya et al in view of Gjerde et al in order to achieve the express advantages, as noted by Cohen et al., of an invention which provides a useful anion exchange resin such as diethylaminoethyl and polyethyleneimine.

9. Claim 16 is rejected under 35 U.S.C. 103(a) as being obvious over Ohmiya et al. (Analytical Biochemistry, (1990), Vol. 189, pages 126-130) in view of Gjerde et al. (U.S. Patent 5,972,222) (October 26, 1999) further in view of Ausserer et al. (Biotechniques, (1995), Vol. 19. No.1, pages 136-139).

Ohmiya et al. in view of Gjerde et al. teach a method of claims 1-4, 7-13, 17-36, 38- 42, 64, 66, 67, and 68 as described above.

Ohmiya et al. in view of Gjerde et al do not teach a method, wherein the solid comprises particles with an average diameter between approximately 2 micron and 10 micron.

Ausserer et al. teaches a method, wherein the solid comprises particles with an average diameter between approximately 2 micron and 10 micron (13 micron to be precise, Page 136, Column 2, lines 8-11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the solid comprises particles with an average diameter between approximately 2 micron and 10 micron of Ausserer et al. in the high-resolution anion exchange chromatographic method of Ohmiya et al in view of Gjerde et al since Ausserer et al. states, "The rapid mass transport characteristics of this resin result in higher efficiency oligonucleotide separations than are possible with traditional

macroporous resins or with reverse-phase columns (Page 136, Column 2, lines 11-14) ". An ordinary practitioner would have been motivated to combine and substitute the method wherein the solid comprises particles with an average diameter between approximately 2 micron and 10 micron of Ausserer et al. in the high-resolution anion exchange chromatographic method of Ohmiya et al in view of Gjerde et al. in order to achieve the express advantages, as noted by Ausserer et al., of an invention which provides a resin with rapid mass transport characteristics, which result in higher efficiency oligonucleotide separations than are possible with traditional macroporous resins or with reverse-phase columns.

Allowable Subject Matter

10. Claims 5 and 33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti , Ph. D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this

Group is (703) 746-4979. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner

May 15, 2003

Arun kr. Chakrabarti

ARUN K. CHAKRABARTI
PATENT EXAMINER